(12) NACH DEM VERTRAG ÜBER DIE INTERNATIONALE ZUSAMMENARBEIT AUF DEM GEBIET DES PATENTWESENS (PCT) VERÖFFENTLICHTE INTERNATIONALE ANMELDUNG

(19) Weltorganisation für geistiges Eigentum
Internationales Büro

(43) Internationales Veröffentlichungsdatum
15. Januar 2004 (15.01.2004)

PCT

(10) Internationale Veröffentlichungsnummer
WO 2004/004750 A3

(51) Internationale Patentklassifikation[7]: A61K 38/00, A61P 37/06, A61K 31/66

(21) Internationales Aktenzeichen: PCT/EP2003/007199

(22) Internationales Anmeldedatum:
4. Juli 2003 (04.07.2003)

(25) Einreichungssprache: Deutsch

(26) Veröffentlichungssprache: Deutsch

(30) Angaben zur Priorität:
102 30 381.9 5. Juli 2002 (05.07.2002) DE

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(81) Bestimmungsstaaten *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Bestimmungsstaaten *(regional)*: ARIPO-Patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), eurasisches Patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), europäisches Patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI-Patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Veröffentlicht:
— *mit internationalem Recherchenbericht*

(88) Veröffentlichungsdatum des internationalen Recherchenberichts: 6. Mai 2004

Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** USE OF ALANYL-AMINOPEPTIDASE INHIBITORS AND PHARMACEUTICAL COMPOSITIONS CONTAINING SAID INHIBITORS

(54) **Bezeichnung:** VERWENDUNG VON INHIBITOREN DER ALANYL-AMINOPEPTIDASEN UND DIESE UMFASSENDE PHARMAZEUTISCHEN ZUBEREITUNGEN

(57) **Abstract:** The invention relates to the use of one or several alanyl-aminopeptidase inhibitors and/or enzyme inhibitors which exhibit the same substrate specificity in order to stimulate the production of TFG-β 1 and the expression of TFG-β 1 in and/or on lymphocyte T regulators. The invention also relates to the use of said inhibitors for preventing and/or curing autoimmune, allergic and cardiovascular diseases and to preclude the rejection of transplants. In addition, said invention relates to applications in which peptidic fragments of pathogenic autoantigens or synthetic analogues and/or specific antigenic components of pathogenic microorganisms are used.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft die Verwendung von einem Inhibitor oder mehreren Inhibitoren von Alanyl-Aminopeptidasen und/oder von Enzymen gleicher Substratspezifität zur Induktion der Produktion von TGF-ß 1 und Expression von TGF-ß 1 in und/oder auf TregZellen und die Verwendung zur Vorbeugung und/oder Behandlung von Autoimmunerkrankungen, Allergien, Arteriosklerose und zur Unterdrückung von TransplantatAbstossungen. Weiter betrifft die Erfindung Verwendungen bei der zusätzlich Peptidfragmente von pathogenen Autoantigenen oder synthetische Analoga und/oder spezifische antigene Komponenten pathogener Mikroorganismen eingesetzt werden.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07199

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/00 A61P37/06 A61K31/66

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, PAJ, WPI Data, BIOSIS, MEDLINE, EMBASE, CHEM ABS Data, SCISEARCH, PHARMAPROJECTS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95/04533 A (ANDRULIS PHARM CORP) 16 February 1995 (1995-02-16) *siehe Zusammenfassung, Seite 1, Absatz 1, Seite 2, Zeilen 3-14 und 26* -----	1-40

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 November 2003	19 02 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Stoltner, A

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP03/07199

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 1 to 40
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 1 to 19 relate to a method for treatment of the human or animal body, the search was carried out on the basis of the alleged effects of the compound or composition.

2. [X] Claims Nos.: 1 to 40
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Sheet

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-40 (in part)

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Box I

1. Claims 1 to 40

Although claims 1 to 19 relate to a method for treatment of the human or animal body, the search was carried out on the basis of the alleged effects of the compound or composition.

2. Claims 1 to 40

The current claims 1 to 40 relate to a disproportionately large number of possible compounds/products/devices/methods, of which only a small proportion are supported by the description in accordance with PCT Article 6 and/or can be regarded as having been disclosed in the application in accordance with PCT Article 5. In the present case the claims lack the proper support and the application lacks the requisite disclosure to such an extent that it appears impossible to carry out a meaningful search covering the entire range of protection sought. The search was therefore directed to the parts of the claims that appear to be supported and disclosed in the above sense, that is the parts relating to the compounds according to examples 1 to 4.

Moreover, claim 1 claims substances which are defined by their function and in which there is no relationship between structure and function. A person skilled in the art thus has no indication which inhibitors are ultimately effective in the prevention or treatment of autoimmune diseases.

The applicant is advised that claims relating to inventions in respect of which no international search report has been established cannot normally be the subject of an international preliminary examination (PCT Rule 66.1(e)). In its capacity as International Preliminary Examining Authority the EPO generally will not carry out a preliminary examination for subjects that have not been searched. This also applies to cases where the claims were amended after receipt of the international search report (PCT Article 19) or where the applicant submits new claims in the course of the procedure under PCT Chapter II. After entry into the regional phase before the EPO, however, an additional search may be carried out in the course of the examination (cf. EPO Guidelines, Part C, VI, 8.5) if the deficiencies that led to the declaration under PCT Article 17(2) have been remedied.

Box II

The International Searching Authority has determined that this international application contains multiple (groups of) inventions, as follows:

1. Claims 1-40 (in part)

   Use of thalidomide as an inhibitor of alanyl aminopeptidases and/or of enzymes of the same substrate specificity to induce the production of TGF-β1 and the expression of TGF-β1 in and/or on Treg cells for the prevention or treatment of autoimmune diseases.

2. Claims 1-40 (in part)

   Use of actinonin for the treatment of autoimmune diseases.

3. Claims 1-40 (in part)

   Use of leuhistin for the treatment of autoimmune diseases.

4. Claims 1-40 (in part)

   Use of phebestin for the treatment of autoimmune diseases.

5. Claims 1-40 (in part)

   Use of amastatin for the treatment of autoimmune diseases.

6. Claims 1-40 (in part)

   Use of bestatin for the treatment of autoimmune diseases.

7. Claims 1-40 (in part)

   Use of probestin for the treatment of autoimmune diseases.

8. Claims 1-40 (in part)

   Use of arphamenine for the treatment of autoimmune diseases.

9. Claims 1-40 (in part)

   Use of MR 387 for the treatment of autoimmune diseases.

10. Claims 1-40 (in part)

Use of β-amino thiols for the treatment of autoimmune diseases.

11. Claims 1-40 (in part)

Use of α-amino phosphinic acids for the treatment of autoimmune diseases.

12. Claims 1-40 (in part)

Use of α-amino phosphonates for the treatment of autoimmune diseases.

13. Claims 1-40 (in part)

Use of α-amino boric acids for the treatment of autoimmune diseases.

14. Claims 1-40 (in part)

Use of α-amino aldehydes for the treatment of autoimmune diseases.

15. Claims 1-40 (in part)

Use of hydroxamates of α-amino acids for the treatment of autoimmune diseases.

16. Claims 1-40 (in part)

Use of *N*-phenylphthalimides for the treatment of autoimmune diseases.

17. Claims 1-40 (in part)

Use of *N*-phenylhomophthalimides for the treatment of autoimmune diseases.

18. Claims 1-40 (in part)

Use of α-keto amides for the treatment of autoimmune diseases.

19. Claims 1-40 (in part)

Use of thalidomide and derivatives thereof for the treatment of autoimmune diseases.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/07199

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9504533 A	16-02-1995	AU 7376494 A	28-02-1995
		WO 9504533 A2	16-02-1995